b) loading one or more physiologically effective substances to be delivered to said mammal into or onto said nanoparticles or both; and optionally

c) providing said loaded nanoparticles in a medium allowing the transport of said nanoparticles to the target within or on said mammal after administration.

BASIS FOR THE AMENDMENTS

The trademark names Genapol[R] and Bauki[R] substances have now been particularly defined consistent with "Enclosures 2 to 4" attached to the Preliminary Amendment of December 13, 2001. Note pages 16-17 of this Preliminary Amendment, incorporated herein by reference.

REMARKS

Favorable reconsideration of this application is requested.

Claims 88-134 are in the case. They stand rejected under 35 U.S.C. § 103 as being unpatentable over either Canal or Bernstein in view of Kreuter and Jans.

The invention relates to a drug targeting system for administration to a mammal, comprising:

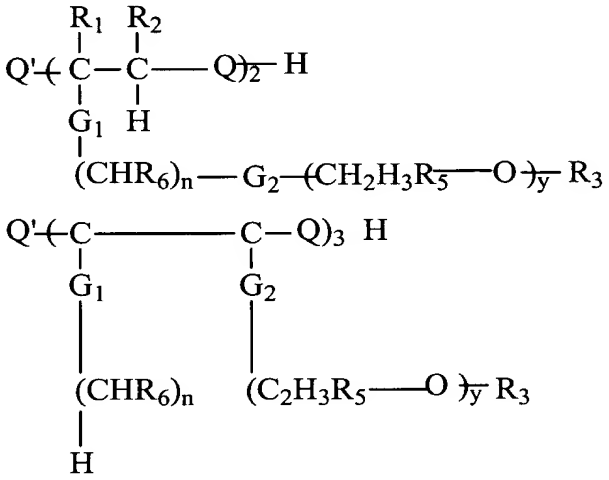
a) nanoparticles made of a polymeric material, said nanoparticles being free of a surfactant surface coating and comprising said polymeric material, one or more physiologically effective substances to be delivered to said mammal, and one or more stabilizers for said nanoparticles for effecting targeting of said one or more physiologically effective substances to a specific site within or on a mammalian body, said one or more stabilizers being selected from the group consisting of polysorbate 85, polysorbate 81,

dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, allcoxylated ethers, alkoxylated esters, alkoxylated mono-, di and trigiycerides, alkoxylated phenols and diphenols, Genapol® compounds, Bauki compounds®, sodium stearate, metal salts of alcohol sulfates and metal salts of sulfosuccinates and mixtures of two or more of said substances, wherein said Genapol^R compounds are of the formula

$$CH_3(CH_2)_y - (O\text{-}CH_2\text{-}CH_2)_x\text{-}OH$$

wherein y is in the range of 4 to 18 and x is in the range of 1 to 18,

and said Bauki^R compounds are of the formulas (I) and (I')



(I)

(I')

in which R_1, R_2, R_5 and R_6 are identical or different and represent hydrogen and a methyl or ethyl group,

Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

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x is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000, if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44, y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms, and

b) a physiologically acceptable carrier, which allows the transport of said nanoparticles to the target within said mammal after administration.

In the claimed invention the nanoparticles are

1. Free of a surfactant surface coating, and

2. The stabilizers are selected from one of the defined substances.

Such a targeting system is suitable for administration to a mammal, it providing a system being to be able to cross the blood brain barrier (bbb). This is neither taught by, nor obvious from the art relied upon by the Examiner.

Thus, Canal, one of the primary references relied upon by the Examiner, discloses

> pharmaceutical compositions in the form of particles comprising a biodegradable polymer and/or a polysaccharide jellifying and/or bioadhesive polymer, an amphiphilic polymer, an agent modifying the interface properties of the particles and a pharmacologically active substance. Said compositions exhibit improved biocompatability features and allow a controlled release of the active substance (Abstract).

In Canal it is essential that there be present an agent modifying the interface properties of the particles. Note, in particular, page 4, lines 25-27, i.e., the surface having active agents as there defined. This is contrary to the express requirements of the claims, i.e., "being free of a surfactant surface coating." Canal thus teaches away from the claimed invention.

Bernstein, the other primary reference relied upon by the Examiner, discloses the use of microparticles in imaging processes for diagnostic purposes. It does not relate to a drug

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targeting system for administering the drugs across the blood brain barrier, as in the claimed invention. Gases, specifically fluorinated gases, such as perfluorocarbons (imaging agents) are incorporated into microparticles formed of biologically degradable polymers, preferably polylactic acid-co-glycolic acid, in combination with a lipid. No disclosure is present in Bernstein for the incorporation of drugs into microparticles or the absorption of drugs into microparticles. Passage of the drug across the blood brain barrier, as is attained by the claimed invention, is neither discussed nor present in this reference. Further, and most significantly stabilizers as particularly defined by the claims are not disclosed by this reference to be incorporated into its microparticles.

In order to cure these basic deficiencies of the primary reference, the Examiner relies on Kreuter and Jans.

Kreuter is discussed in the specification, Applicants' invention being an improvement thereover. Specifically, essential to the invention of Kreuter is that their nanoparticles be coated with a surfactant. The presence of such a surfactant surface coating is specifically precluded by the claims. It is due to the stabilizers in the nanoparticles of the invention being as defined that a surfactant coating, as in Kreuter, can be omitted and is unnecessary. This manifestor is not obvious, it being contrary to the teaching of Kreuter.

In Kreuter, only nanoparticles being coated with a surfactant may enable the drug present in the composition to pass across the blood brain barrier. In contrast thereto, the inventive nanoparticles do not have a surfactant surface coating, yet, due to the stabilizer being as particularly defined, can effect passage across the blood brain barrier. Due to the blood brain barrier being crossed by simpler nanoparticles, such allows a better control of conditions, reducing side effects and making the passage step more effective.

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The same is true for Bernstein, this reference also not being concerned with passage of its diagnostic substance across the blood brain barrier, its coated microparticles also not containing a stabilizer as particular defined by the claims. Thus, combining the teaching of Kreuter with this reference, the claimed invention is not made obvious thereby.

Jans is even less relevant. It is directed to compositions containing Nebivolol as the active ingredient in micronized form, which has to be incorporated into a solid galenic dosage form, such as tablets, capsules, powders, etc. and semi-solid dosage form like creams or gels. The fact that various polysorbates, as disclosed by Jans, are known clearly does not make obvious nor suggest their incorporation into a particular target system as claimed whereby unobviously superior properties and results are obtained.

In summary, in the claimed targeting system the nanoparticles are free of a surfactant surface coating, contrary to the express requirements of the prior art, such being possible due to the stabilizers being as critically defined in the claims. Applicants' discovery, providing for a solution of being able to omit a surfactant surface coating onto nanoparticles due to the presence of the particular stabilizers as claimed is neither taught by, nor obvious from the art.

Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. § 103 is requested.

With regard to the rejection of the claims under 35 U.S.C. § 112, second paragraph, the definitions of the Trade name products have now been incorporated into the claims.

Consequently, withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph, is thus requested.

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It is submitted that this application is now in condition for allowance and which is solicited.

Respectfully submitted,

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MARKED-UP COPY

IN THE SPECIFICATION

Page 16, lines 9-23, please amend as in the attached marked-up copy to read as follows:

Specifically advantageous drug targeting systems according to the invention contain nanoparticles, wherein said stabilizer comprises a substance selected from the group consisting of polysorbate 85, dextran 12.000, carboxylic acid esters of multifunctional alcohols, polysorbates, poloxameres, poloxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol^{R} and Bauki^{R} series, metal salts of carboxylic acids, metal salts of alcohol sulfates and metal salts of sulfosuccinates and mixtures of two or more of said substances, wherein said Genapol^{R} compounds are of the formulas

$CH_3(CH_2)_y - (O-CH_2-CH_2)_x-OH$

wherein y is in the range of 4 to 18 and x is in the range of 1 to 18

and said Bauki^{R} compounds are of the formulas (I) or (I')

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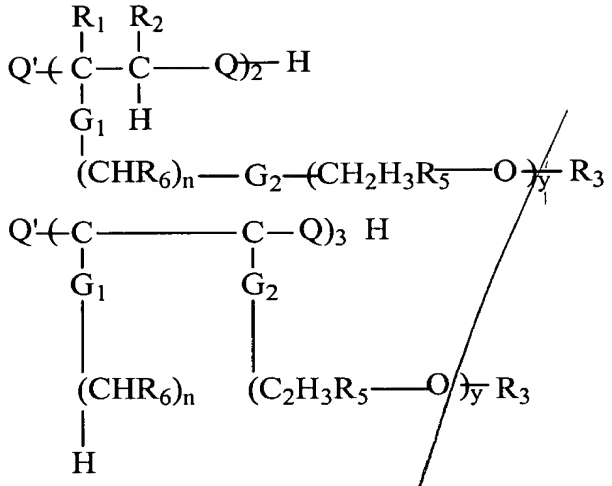

(I)

(I')

in which R_1, R_2, R_5 and R_6 are identical or different and represent hydrogen and a methyl or ethyl group,

Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

x is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000 if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44,

y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms.

For example, said stabilizer comprises a substance selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12.000, carboxylic acid esters and preferably fatty acid esters of glycerol and sorbitol, even more preferably glycerol monostearate, sorbitan monostearate and sorbitan monooleate, poloxamer 188 (Pluronic^R F68), ethoxylated ethers, ethoxylated esters, ethoxylated triglycerides, ethoxylated phenols and diphenols, metal salts

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of fatty acids and metal salts of fatty alcohol sulfates, preferably sodium salts of fatty acids and of fatty alcohol sulfates, even more preferably sodium stearate and sodium lauryl sulfate and mixtures of two or more of said substances.

IN THE CLAIMS

--88. (Amended) A drug targeting system for administration to a mammal, comprising:

a) nanoparticles made of a polymeric material, said nanoparticles being free of a surfactant surface coating and comprising said polymeric material, one or more physiologically effective substances to be delivered to said mammal, and one or more stabilizers for said nanoparticles for effecting targeting of said one or more physiologically effective substances to a specific site within or on a mammalian body, said one or more stabilizers being selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di and triglycerides, alkoxylated phenols and diphenols, Genapol^{R} compounds, Bauki compounds^{R}, sodium stearate, metal salts of alcohol sulfates and metal salts of sulfosuccinates and mixtures of two or more of said substances, wherein said Genapol^{R} compounds are of the formula

$CH_3(CH_2)_y - (O-CH_2-CH_2)_x-OH$

wherein y is in the range of 4 to 18 and x is in the range of 1 to 18

and said Bauki^{R} compounds are of the formulas (I) and (I')

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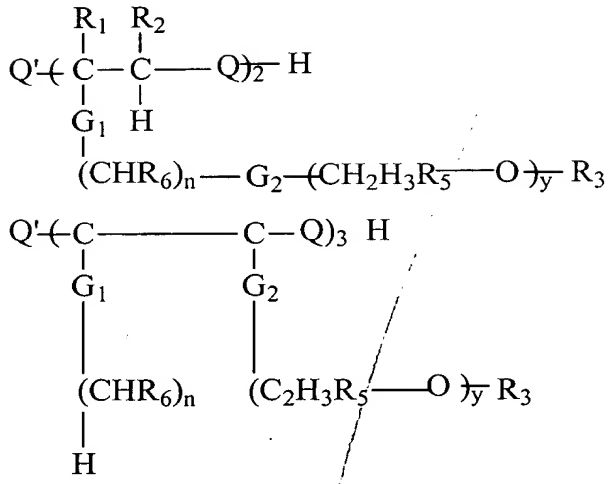

(I)

(I')

in which R_1, R_2, R_5 and R_6 are identical or different and represent hydrogen and a methyl or ethyl group,

Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

x is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000, if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44, y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms, and

b) a physiologically acceptable carrier, which allows the transport of said nanoparticles to the target within said mammal after administration.

101. (Amended) A method for preparing a drug targeting system for administering one or more physiologically effective substances to a mammal, said method comprising:

a) preparing nanoparticles made of a polymeric material, said nanoparticles being free of a surfactant surface coating and comprising said polymeric material, one or more

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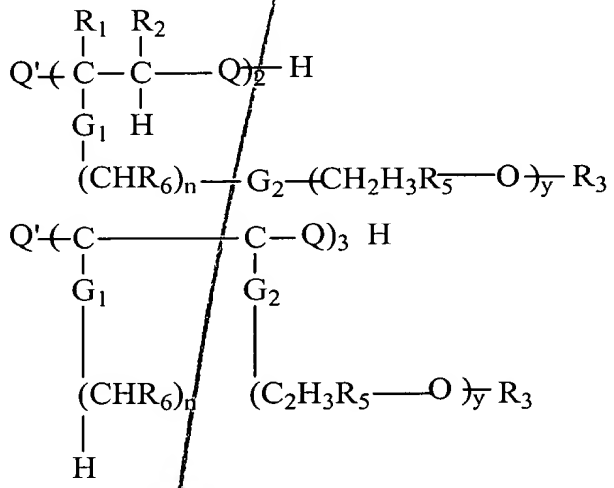
physiologically effective substances to be delivered to said mammal, and one or more stabilizers for said nanoparticles allowing targeting of said one or more physiologically effective substances to a specific site within or on a mammalian body, said one or more stabilizers being selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxarnines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di and triglycerides, alkoxylated phenols and diphenols, Genapol^{R} compounds, Bauki compounds^{R}, sodium stearate, metal salts, of alcohol sulfates and metal salts of sulfosuccinates and mixtures of two or more of said substances, wherein said Genapol^{R} compounds are of the formula

$CH_3(CH_2)_y$ - $(O\text{-}CH_2\text{-}CH_2)_x$-OH

wherein y is in the range of 4 to 18 and x is in the range of 1 to 18

and said Bauki^{R} compounds are of the formulas (I) and (I')



(I)

(I')

in which R_1, R_2, R_5 and R_6 are identical or different and represent hydrogen and a methyl or ethyl group.

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Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

x is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000, if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44,

y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms, and; by polymerizing one or more monomeric or oligomeric precursors of said polymeric material or both, in the presence of said one or more physiologically effective substances and in the presence of said stabilizers; and optionally

b) providing said nanoparticles in a medium allowing the transport of said nanoparticles to a target within or on said mammal after administration.

102. (Amended) A method for preparing a drug targeting system for administering one or more physiologically effective substances to a mammal, said method comprising:

a) preparing nanoparticles made of a polymeric material, said nanoparticles being free of a surfactant surface coating and comprising said polymeric material and one or more stabilizers for said nanoparticles, said one or more stabilizers being selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono, di and triglycerides, alkoxylated phenoles and diphenoles, Genapol^R compound, Bauki compounds^R, sodium stearate, metal salts of alcohol sulfates and metal salts of sulfosuccinates and mixtures of two or more of said substances, wherein said Genapol^R compounds are of the formula

$CH_3(CH_2)_y - (O-CH_2-CH_2)_x-OH$

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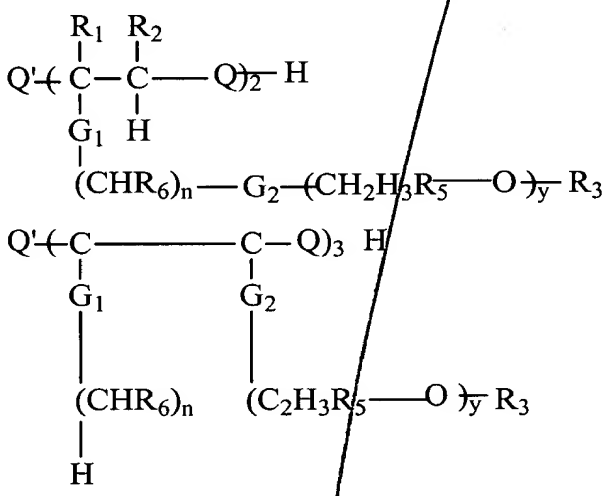
wherein y is in the range of 4 to 18 and x is in the range of 1 to 18

and said Bauki^R compounds are of the formulas (I) and (I')



(I)

(I')

in which R_1, R_2, R_5 and R_6 are identical or different and represent hydrogen and a methyl or ethyl group,

Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

x is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000, if Q is an ester or amide function, G_1 and G_2 are a valency, oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44,

y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms, and; by polymerizing one or more moriomeric or oligomeric precursors of said polymeric material or both, in the presence of said stabilizers;

b) loading one or more physiologically effective substances to be delivered to said mammal into or onto said nanoparticles or both; and optionally

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c) providing said loaded nanoparticles in a medium allowing the transport of said nanoparticles to the target within or on said mammal after administration.--

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